CORRESPONDENCE

Breast Density and Cancer

The decrease in the radio-opaque density of mammograms by 6.1% in healthy, lean (body mass index <23) women, 30–65 years of age, who were fed a low-fat diet for 2 years *(1)* suggests that environmental factors modulate mammary parenchymal metabolism. However, it is unclear whether these findings are applicable to the individual woman in the detection of breast cancer.

In the Dom study of 23 311 postmenopausal Dutch women, which investigated the radiologic aspects of breast structure, de Waard *(2)* concluded that, from puberty on, breast abnormalities increase unless counteracted by pregnancy and that dysplasia in women with a pregnancy after 35 years of age involved luteal insufficiency. Furthermore, de Waard et al. *(3)* reported that a family history of breast cancer increased the positivity rate of mammary screening (relative risk [RR] = 2.2 positive/negative).

While the accuracy of screening varies among studies, it should be noted that 1) only 15% of the volume of breasts of premenopausal women consists of epidermal cells, 2) mammary dysplasia is not associated with estrogen receptor concentration *(4)*, and 3) breast cancer develops in a large number of women who do not have radiologic abnormalities *(5)*.

While mammary dysplasia is modified by fat intake *(6)*, exercise *(7)*, and diet *(1)*, it is unclear how changes during pregnancy reverse adverse changes in mammary parenchyma.

Because the expression of estrogen receptors and mammary mitotic cycling are established at puberty *(8,9)*, development of growth patterns of mammary tissue prior to puberty may ''set'' the future risk. Since the risk of breast cancer is associated with birth weight *(10)* and adult height *(11)*, it is significant that 1) a low birth weight (<3000 g) increases the risk of preeclampsia later in life *(12)*, 2) perinatal characteristics are associated with high-risk mammographic patterns *(13)*, and 3) daughters born after an eclampsia/preeclampsia pregnancy have a lower risk of breast cancer *(14)*, supporting the importance of fetal growth patterns. If cancer develops as a failure of the host organs to exercise growth control, mammary dysplasia should be associated with growth factor production *(15)*.

While increasing density in breast parenchyma from none to more than 73% of the area in patients increases the RR by 6.05 (95% confidence interval = 2.82–12.97) *(5)*, a large proportion of women with screening-detected breast cancers may experience no benefit from treatment because their disease may never progress or may even regress if left undetected *(16,17)*.

With the more rapid tumor growth in women under 35 years with stage II node-positive disease (approximately 11% of breast cancer cases) *(18)*, it would be of interest to determine the increase in mammary dysplasia and growth factor profile in such selected patients. Furthermore, in premenopausal, healthy women requesting a reductive mastectomy, measurement of the mitotic index and mammary parenchymal and serum growth factor profiles could give leads to the relation of breast density and growth rate, especially inasmuch as reductive mastectomy may decrease the risk of breast cancer *(19)*.

Modification of the lifestyle of postmenopausal women may alleviate breast cancer, but prevention may involve modification of fetal dysfunctions and their modulation during puberty. Much needs to be done in the study of breast density, since 50% of women who develop this disease will continue to die from it despite the use of mammography.

PETER HILL

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Note

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Re: Risk Factors for Lung Cancer and for Intervention Effects in CARET, the Beta-Carotene and Retinol Efficacy Trial

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study *(1)* and the Beta-Carotene and Retinol Efficacy Trial (CARET) *(2)* showed an excess of lung cancer in supplemented individuals at high risk of developing this complication (e.g., smokers). From a reanalysis of their data, Omenn et al. *(2)* concluded that these subjects should be discouraged from taking β-carotene; however, in their recommendation, they did not address the issue of alcohol consumption. Similarly, in a comment on their ATBC Study, Rautalahti et al. *(3)* mention six possible explanations for the complication, but they do not include alcohol as a possible contributory factor. It should be pointed out, however, that alcohol has been reported to increase β-carotene levels in men *(4)*, women *(5)*, nonhuman primates *(6)*, and rats *(7);* this increase in β-carotene levels may be of relevance because of a possible dose effect for the above noted complication. Furthermore, in the nonhuman primates, there was associted hepatotoxicity, including striking ultrastructural lesions and an increase in circulating transaminases *(7)*. Since heavy smokers are commonly also drinkers, we questioned *(8)* whether the complication could have been exacerbated by ethanol and, specifically, whether the excess of lung cancer might have occurred predominantly, or even exclusively, in those smokers who were also drinkers. Subsequently, this hypothesis was verified in a reanalysis of the ATBC Study *(9);* this reanalysis revealed the complication to be associated with alcohol drinking. Actually, the data of Omenn et al. *(2)* also showed a statistically significant difference between the nondrinkers and persons consuming substantial amounts of alcohol, albeit with a less consistent dose–response effect. Furthermore, in both of these clinical and experimental studies, a similar preparation of β-carotene was apparently used, i.e., β-carotene incorporated into beadlets. These beadlets were found to augment the hepatotoxic interactions between ethanol and β-carotene *(7,10)*, with exacerbation of the ultrastructural changes in the mitochondria, the associated release of mitochondrial enzymes into the circulation, and the proliferation of the smooth endoplasmic reticulum. The beadlets contain various additives, but the compound responsible for the toxicity has not yet been identified.

Another postulated mechanism for toxicity is the oxidative attack of β-carotene by heavy smoking *(11)*. It is interesting that ethanol is also known to cause significant oxidative stress *(12)*, incriminated in many adverse effects, including promotion of carcinogenesis. Furthermore, in CARET, retinol was administered at the same time *(1,9)*, and it may also have contributed to the toxicity, since studies in rats *(13)* and humans *(14)* revealed that the combination of ethanol and vitamin A results in hepatotoxicity not seen with the same dosage of either compound alone.

Contrasting with the findings of the ATBC Studies *(1)* and CARET *(2)*, a study by Henneken et al. *(15)* found no comparable complications. However, Henneken et al. used a lower dose and a different β-carotene preparation. Moreover, no alcohol consumption data were given, but there was a much lower incidence of smokers and, hence, presumably of drinkers. Obviously, further analysis is needed, but it is now appropriate, whenever supplementation of β-carotene is being considered, to warn of the possible hazards from concomitant drinking of substantial amounts of alcohol.

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Notes

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Response

We welcome the suggestions from Drs. Leo and Lieber about potential explanations for the adverse effects of beta-carotene in the ATBC Study and CARET. These studies *(1,2)* of known dosages in humans found more than one excess lung cancer per 1000 persons exposed per year; in the usual regulatory framework of the U.S. Environmental Protection Agency and the Food and Drug Administration (FDA), this incidence is the equivalent of almost 70 000 per million exposed over a presumed 70-year lifetime. Thus, the FDA, the National Toxicology Program of the National Institute of Environmental Health Sciences–National Institutes of Health, and the International Agency for Research on Cancer of the World Health Organization are all considering the evidence for carcinogenicity of this chemical agent.

The self-reported levels of alcohol intake in Finland and in the United States associated with higher β-carotene- or β-carotene-plus-retinol-related lung cancer risk in the active treatment arms of these trials *(1,2)* are much lower than the levels studied by Leo and Lieber *(3)* and others *(4)*. None of our trial participants was a known alcoholic; previous liver disease was a criterion for exclusion in CARET. We have reported that there was no detectable increase in serum aspartate aminotransferase (AST) and only a modest, nonprogressive increase in alkaline phosphatase levels in the active arm. We further report now that, in the subset of CARET participants in whom AST and alkaline phosphatase levels were routinely monitored, serum concentrations of AST (but not alkaline phosphatase) in the placebo arm were statistically significantly associated with self-reported alcohol intake, whereas in the active arm there were no statistically significant associations between serum concentrations of these enzymes and alcohol intake (Table 1). The concentrations of these enzymes were low relative to those reflective of liver damage; only about 1% of measured concentrations of AST and alkaline phosphatase exceeded 100 IU/L or 195 IU/L, respectively. Furthermore, while in the placebo arm there was a suggestion of increased serum β-carotene concentration with increased alcohol intake (not statistically significant), in the active arm there was a statistically significant inverse association between alcohol intake and serum β-carotene concentration. We long ago inquired of Hoffmann-La Roche (Nutley, NJ) about additives and impurities in the β-carotene beadlets and commissioned an independent toxicologic review by Dr. David Kalman of the University of Washington Department of Environmental Health. No suspect chemicals were identified.

We certainly affirm the recommendation by Leo and Lieber that "substantial" alcohol intake should be strongly discouraged, in accord with Healthy People 2000 recommendations from the U.S. Public Health Service *(5)*.

GILBERT S. OMENN AND CARET CO-INVESTIGATORS AND STAFF

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Note

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Table 1. Means and 95% confidence intervals for serum concentrations of aspartate aminotransferase (AST), alkaline phosphatase, and β-carotene by reported alcohol intake at the first assessment of dietary intake in participants in the Beta-Carotene and Retinol Efficacy Trial (CARET) with postrandomization measurements of these analytes

	AST, IU/L†		Alkaline phosphatase, IU/L†		β-Carotene, ng/mL†	
Alcohol intake*	Active	Placebo	Active	Placebo	Active	Placebo
Nondrinkers	22.9 (21.5–24.3)	22.7 (21.7–23.6)	94.8 (91.4–98.2)	91.2 (87.6–94.9)	2730 (2510–2950)	188 (170–206)
Drinkers, below median of alcohol intake	24.6 (23.0–26.2)	22.8 (20.4–25.1)	93.5 (89.0–97.9)	91.3 (86.4–96.2)	2770 (2490–3060)	237 (156–317)
Drinkers, third quartile of alcohol intake	24.6 (23.3–25.9)	23.6 (22.4–24.8)	93.8 (90.5–97.1)	85.1 (80.8–89.4)	2430 (2210–2650)	240 (172–309)
Drinkers, fourth quartile of alcohol intake	24.7 (23.5–25.9)	28.0 (24.6–31.4)	91.1 (86.5–95.7)	84.9 (80.3–89.5)	2410 (2170–2650)	204 (159–248)
Correlation (*P* value)	.06 (.12)	.18 (.0001)	−.04 (.26)	−.07 (.16)	−.13 (.0002)	−.02 (.74)

*In the whole CARET population, 33% of men and 39% of women reported no alcohol intake. Percentiles of alcohol intake for men are median 3.0 g/day and 75th percentile 18.7 g/day; for women, they are median 1.2 g/day and 75th percentile 11.1 g/day. An alcoholic drink contains approximately 15 g alcohol.

†Unless otherwise specified, values in columns = means (95% confidence intervals).

Re: Saturated Fat Intake and Lung Cancer Risk Among Nonsmoking Women in Missouri

Several *(1–8)*, but not all *(9–12)*, epidemiologic studies indicate that consumption of fat-rich diets increases risk of lung cancer. In 1993, we reported *(13)* a pronounced association between dietary fat and lung cancer risk. In a large, population-based, case–control study of nonsmoking Missouri women, risk of lung cancer increased across increasing levels of saturated fat intake. The odds ratio (OR) was more than sixfold greater for the highest quintile of consumption compared with the lowest quintile. We have since found that the ORs vary substantially according to the method of energy adjustment. In this correspondence, we report ORs based on two regression models other than the one used in the original analysis. The significantly elevated risk associated with saturated fat intake was not eliminated under these two models; however, the magnitude of most of the risk estimates and the consistency of a trend were clearly reduced using the alternative methods of energy adjustment (Table 1). For the reasons noted below, we believe our original estimates of risk were inflated and those resulting from the other methods are more valid.

The high correlation between saturated fat and total calories makes it difficult to assess the effect of saturated fat independent of its association with energy. In our original analysis *(13)*, we entered both saturated fat and total calories as categorical variables in a standard multivariate model, since the nutrient residual method did not appear to offer any advantage. As others *(14–16)* have noted, the linear nutrient residual model is equivalent to the linear standard multivariate model. Furthermore, residuals do not convey an intuitive sense of nutrient intake, such as grams or calories of saturated fat consumed. At the time, we did not appreciate that the equivalence of the two methods ended when the nutrient intake data were categorized, a standard practice in epidemiologic studies.

As Brown et al. *(17)* and others *(18)* noted, when estimating the effect of increasing intake from dietary fat while keeping total energy intake constant (substitution effect), the standard multivariate model exaggerates the true variation in fat intake when data are modeled as quantile-categorical variables. Because the variability of the nutrient residuals provides a better estimate of the true variation in the nutrient of interest when total energy intake is fixed, the quantiles of the residual distribution provide a more valid description of the actual ORs to be expected when changing dietary composition. The multivariate nutrient density approach has the added advantage of being readily interpretable, representing the effect of changing the percentage of fat (or saturated fat) in the diet while keeping total energy intake constant.

Despite years of discussion about energy adjustment methods, we noted that only two observational studies of dietary fat and lung cancer *(12,13)* used any method of energy adjustment. In part, this circumstance reflects the fact that both the rationale and the appropriate method of energy adjustment remain controversial *(19,20)*. In summary, computer simulations *(17)* and two analytic studies of dietary fat and cancer risk *(13,21)* now provide evidence that risk estimates and subsequent conclusions can be profoundly influenced by the method of energy adjustment.

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Table 1. Odds ratios (with 95% confidence intervals) of lung cancer among nonsmoking Missouri women according to quintiles of saturated fat intake: effect of energy adjustment method

	Quintile of saturated fat calories					
Energy adjustment method*	1	2	3	4	5	*P* for trend
Standard multivariate†	1.0‡	1.66 (0.94–2.93)	1.82 (0.97–3.44)	2.89 (1.38–6.07)	6.27 (2.68–14.6)	<.0001
No. of case subjects/No. of control subjects	67/204	78/205	88/206	81/202	115/204	
Nutrient residual§	1.0‡	1.46 (0.86–2.51)	1.72 (1.01–2.92)	1.95 (1.16–3.30)	1.78 (1.04–3.04)	.02
No. of case subjects/No. of control subjects	57/204	64/204	87/205	110/204	111/204	
Multivariate nutrient density‖	1.0‡	1.86 (1.09–3.18)	1.63 (0.92–2.89)	2.24 (1.31–3.85)	2.38 (1.35–4.17)	.003
No. of case subjects/No. of control subjects	52/204	92/204	60/205	107/204	119/204	

*All three methods include as confounders age (continuous), smoking history (never smoked = 0; former smoker = 1), previous lung disease (no = 0; yes = 1), interview type (direct = 0; proxy = 1), and intakes of total calories, citrus fruits and juice, and beans and peas (quintiles).

†Independent variables include calories from saturated fat and total calories as categorical variables. Results originally reported in 1993 *(13)*.

‡Reference category.

§Independent variables include residual calories as a categorical variable. Residual calories = observed saturated fat kcal − (estimated saturated fat kcal). In a linear model, estimated saturated fat kcal = $\alpha + \beta$ total kcal. The indicator variables are derived from the continuous residual values.

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Re: Correlating Nutrition to Recent Cancer Mortality Statistics

Wynder and Cohen *(1)* attribute the declining mortality from breast, prostate, and colon cancers *(2)* as well as from cardiovasular disease *(3)* to the reduction of total fat intake in the U.S. population in recent decades. The authors are fully aware of the differential effect of saturated, polyunsaturated, and monounsaturated fat on physiologic parameters and human disease risk—in fact, they have been major scientific contributors in this area. From the perspective of the U.S. population, it may make little difference to focus on total rather than saturated fat, although evidence incriminating saturated fat is strong for prostate cancer but weaker for cardiovascular disease and colorectal cancer and weaker still for breast cancer. The dominance, however, of the English language scientific and general press in the world scene has adversely affected the attitudes toward total fat intake in the Mediterranean countries in which most of the total fat is monounsaturated and is in the form of olive oil *(4)*. There is strong evidence that consumption of olive oil may convey substantial protection against coronary heart disease *(5)*, and several studies have indicated that it may also provide some protection against breast cancer *(6)* and possibly other forms of cancer *(7)* and even against osteoporosis *(8)*. Mediterranean countries have lower rates of occurrence of these diseases and conditions in comparison to the United States, even though total fat intake has been as high or higher than that in the United States. The overall evidence points to a beneficial effect of olive oil on human health. Although the data may not be strong enough to dictate substitution of olive oil for other types of lipids in populations who do not traditionally consume it, they strongly suggest that the Mediterranean populations should not risk diverting from their olive oil-centered dietary habits.

Dietary guidelines have been widely perceived as indicating that total fat intake should be reduced. "Total fat," however, is not a very useful term, because fats and oils are distinct categories in the broad group of lipids. It should be made clear that the evidence for the negative effects of dietary fat, such as it is, does not apply to monounsaturated triglycerides that dominate olive oil.

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Notes

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Response

Drs. Trichopoulou and Lagiou make a valid and interesting point. Our focus on secular changes in total fat consumption as a possible cause of the recently observed decrease in U.S. cancer mortality rates actually refers to a population (North America) in which olive oil plays a relatively minor role in the diet. Clearly, a unique feature of the Mediterranean diet is its reliance on olive oil, and there is mounting epidemiologic and experimental evidence that olive oil may provide some reduction in the risk of a variety of chronic diseases including heart disease, cancer, diabetes, and perhaps osteoporosis. It should be noted, however, that there are other components of the Mediterranean diet that may also confer protection, such as high consumption of tomatoes, grains, nuts, fruit, and yogurt, as well as a lower consumption of animal fats and vegetable oils, rendering it difficult to single out the effects of olive oil per se. Nonetheless, Drs. Trichopoulou and Lagiou are correct in pointing out that our emphasis on secular changes in total fat consumption as the possible cause of the recent drop in U.S. cancer mortality rates may not be generalizable to other countries, particularly those such as Greece and Spain in which olive oil plays a central role in the diet.

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Re: Relationship Between Lifetime Ovulatory Cycles and Overexpression of Mutant p53 in Epithelial Ovarian Cancer

Schildkraut et al. *(1)* recently reported an association between number of lifetime ovulatory cycles and the risk of p53-overexpressed invasive epithelial ovarian cancer, but not of p53-negative cancer. From the data they presented, I conclude exactly the opposite: p53-positive and p53-negative cancers are equally associated with ovulation-related risk factors, the sole exception being age at diagnosis, which was on average some 3 years greater for the p53-positive case subjects. The study participants were all less than 55 years of age at diagnosis/interview; the majority were premenopausal or perimenopausal. Schildkraut et al. estimated the number of lifetime ovulatory cycles from a linear combination of five factors: age at most recent menstrual period (''index age''), age at menarche, and total durations of pregnancies, breastfeeding, and oral contraceptive use. None of the last four mentioned factors differed significantly between the p53-positive and p53-negative case subjects [P = .71, .14, .06, and 0.23, respectively *(1)*]. Comparing p53-positive and p53-negative cancers, the decreasing odds ratio trends with increasing months pregnant were very close *(1)*, consistent in magnitude with the protective trends seen for parity in many other studies *(2,3)*. Similarly, p53-positive and p53-negative cancers had virtually identical odds ratio trends with duration of oral contraceptive use *(1)*, again of the same magnitude as seen elsewhere *(2,3)*. Age at menarche and duration of breastfeeding contributed very little to the variation in number of ovulatory cycles *(1)*. Thus, only index age is responsible for the purported difference in risk according to lifetime ovulatory cycles.

Furthermore, the authors' adjustment for continuous age terms need not remove the age effect present in the categories of lifetime ovulatory cycles. It is straightforward to show that, even with adjustment for age as a continuous term, age at diagnosis can completely account for the pattern of odds ratios in lifetime ovulatory cycles seen by Schildkraut et al.

While the suggested biologic rationale—that p53 overexpression indicates ovulatory proliferation-induced, preneoplastic DNA damage *(4)*—is attractive, the data of Schildkraut et al. provide evidence to the contrary, that p53 overexpression more likely results from damage occurring during neoplastic proliferation of the tumors. They show that, in addition to older age at diagnosis, p53-positive tumors are more likely to be of poorer differentiation than p53-negative tumors ($P<10^{-5}$) and of distant rather than local–regional stage at diagnosis (P = .0002) *(1)*. These well-known features *(4–6)* thus indicate that p53-positive cancers are those diagnosed later in the neoplastic process, when more genetic errors have accumulated. Therefore, the results do *not* provide evidence for p53-specific causal mechanisms in the pathogenesis of ovarian cancer.

Finally, Schildkraut et al. *(1)* state that pregnancy, oral contraceptive use, and lactation all convey their protective effects only through anovulation. However, the number of analyzed case subjects (n = 197) provided insufficient study power to make this conclusion. Ovulation may be involved in the disease process, but it cannot be the entire mechanism *(7)*. Simply put, the reduction in risk with parity [odds ratio = 0.83 for each successive pregnancy *(2)*] is just too strong compared with the fraction of ovulatory years prevented, at most 5% per pregnancy (i.e., odds ratio = 0.95); these odds ratios are statistically incompatible [two-sided Wald test, $P<10^{-5}$, using the data summarized by Whittemore et al. *(2)*] and remain so even accounting for latency *(8,9)*. How ''incessant'' ovulation is actually involved in ovarian cancer pathogenesis remains a very interesting question, certainly beyond the idea of ovulatory wound repair and accompanying cellular proliferation.

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Response

In our recent article *(1)*, we concluded that exposure to a high number of ovulatory cycles was associated with an increased risk of developing ovarian cancers that overexpress p53. Although the data that we presented were adjusted for various potential confounders, including age, Dr. Risch suggests that all the variation in ovulatory exposure may be explained by age. Dr. Risch also suggests that the relationship between age and p53-positive ovarian cancer is explained by the association between late stage ovarian cancer and p53 overexpression and is a result of tumor progression.

Because of the issues raised by Dr. Risch, we conducted a paired-matched, case–control analysis applying a conditional logistic regression model. Control subjects were matched to the p53-positive ovarian cancer patients on the basis of ''exact'' age and Surveillance, Epidemiology, and End Results (SEER) registry[1] in a ratio of 4:1 to achieve a sufficient statistical power. Because of the excess number of available control subjects, we were able to achieve exact age matches for all 105 p53-positive ovarian cancer patients. Odds ratios for medium (versus low) ovulatory cycle exposure and high (versus low) ovulatory cycle exposure were 4.9 (95% confidence interval [CI] = 1.4–17.6) and 15.8 (95% CI = 3.8–66.0), respectively. Thus, these results, matched by age and controlling for menopausal status and nulliparity, are consistent with those of our original article and strengthen our conclusion concerning the relationship between ovulatory cycle exposure and ovarian cancer.

We also compared the p53-positive ovarian cancer patients with control subjects, according to stage, and found a relationship between ovulation and case–control status, regardless of stage. For women diagnosed with local or regional disease, controlling for age, menopausal status, and nulliparity, adjusted odds ratios for medium (versus low) and high (versus low) ovulatory cycle exposure were 3.2 (95% CI = 0.4–27.2) and 6.5 (95% CI = 0.6–71.0), respectively. For women with advanced disease, adjusted odds ratios were 6.7 (95% CI = 1.1–42.2) and 13.8 (95% CI = 2.0–95.5) for medium (versus low) and high (versus low) ovulatory exposure, respectively. Another plausible interpretation of the association between p53 mutations and advanced stage is that ovarian cancers have a more aggressive behavior because of their p53 status and are therefore more likely to be detected at an advanced stage. However, the biologic basis for the association between p53 and advanced stage ovarian cancer has not been established, and caution must be taken when interpreting this relationship, since precursor lesions for ovarian cancer remain undefined.

Although these additional analyses strengthen our original conclusion concerning ovulation and the risk of developing ovarian cancer, a larger study that is also representative of older, postmenopausal women with ovarian cancer is needed to confirm our current findings and to achieve a better understanding of the pathogenic processes leading to this disease.

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Reference

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[1]*Editor's note:* SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

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Re: Carcinogenicity of the Drinking Water Mutagen 3-Chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone in the Rat

Komulainen et al. *(1)* recently reported dose-dependent tumor incidence in seven distinct tissues of male and female Wistar rats that had consumed drinking water containing 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone (MX). They suggested cautiously that MX should be studied as a candidate risk factor to explain a ''possible association between consumption of chlorinated drinking water and cancer in humans,'' but they noted specifically that their findings ''cannot be extrapolated to humans.'' However, in their accompanying editorial, Melnick et al. *(2)* proceeded with just such an extrapolation. They estimated potential cancer risks to humans from MX in drinking water and compared these risks with those from two other disinfec-

tion products (i.e., bromodichloromethane and chloroform). They acknowledged that their estimates were dependent on a number of assumptions about the validity of extrapolating from laboratory animals to humans, but although they state that ''there is no information that would indicate that these assumptions are inappropriate,'' there is little evidence that they *are* appropriate. Multisite carcinogenicity of putative carcinogens is not exceptional *(3,4)*, and we note that that there is no generally accepted explanation as to why the tumors in rats occur at different sites. Perhaps MX affects p53 or converts different proto-oncogenes to activated oncogenes. At present, however, these speculations are unverified.

In any case, it would have been helpful if Melnick et al. had reported not just the upper bounds (presumably 95% confidence limits) for the MX and other disinfection products' unit cancer risks but also the corresponding point estimates and their standard errors. Such reporting would have enabled the readers to derive point estimates of MX potencies (i.e., the ratios of the estimated exposure-specific risks) and their 95% confidence limits. Those limits, and any upper bound potency estimates based on them, are certainly of interest, but they are not the same as the ratios of the upper-bound unit cancer risks that were quoted in the editorial *(2)*. The latter could be seriously misleading.

To date, MX has been detected in drinking water in Finland *(5)*, the U.K. *(6)*, The Netherlands *(7)*, the United States *(8)*, Canada *(9)*, Japan *(10)*, China *(11)*, and Russia *(12)*. It seems likely that MX may be found in any country where raw water rich in humic material is chlorinated. Prospective epidemiologic studies could, in principle, determine whether associations exist between measured MX concentrations in drinking water and cancer incidence in humans. But such studies are likely to require decades of research before interpretable results would become available. If it were possible to make realistic estimates of past MX levels, then retrospective epidemiologic studies might provide a shortcut. Alternatively, historical reconstruction of the net mutagenicity of drinking water, as pioneered by the Finnish researchers *(13–15)*, may be a promising approach. In the meantime, we suggest that comments on the public health implications of the challenging results reported by Komulainen et al. *(1)* should be tempered by caveats that reflect the considerable gaps in current knowledge.

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Notes

Editor's note: Drs. Komulainen *(2)* and Melnick *(1)* declined to comment.

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Re: Benzene and the Dose-Related Incidence of Hematologic Neoplasms in China

A recent study *(1)* of workers in Chinese factories clearly demonstrated that exposure to benzene at even low concentrations was associated with an appreciable hazard of blood dyscrasia. Because gasoline in some countries contains benzene in concentrations ranging from trace amounts to as high as 30%, we have investigated the hematologic consequences of exposure to benzene in unofficial vendors of gasoline and motor mechanics in the north of Nigeria *(2)*.

Although Nigeria is one of the largest oil-producing countries, modern filling stations are few and are mostly located in the large cities. When gasoline is in short supply, numerous roadside vendors mushroom along the city routes, and such facilities are common in rural areas.

Our study subjects were male and included 118 roadside vendors of gasoline, 57 mechanics working in small workshops, 38 attendants serving at modern gasoline stations, and 129 control subjects who were not occupationally exposed to gasoline. The roadside vendors were highly important from the study point of view and were divided into three groups. The first group (n = 46) sold only gasoline. The second group (n = 52) sold both gasoline and heavy engine oil for addition to the fuel of motorcycles. Both of these groups lacked any pump. The vendors sucked the gasoline by mouth through rubber hoses from barrels and then siphoned it into motor vehicles. They served between five and 50 customers per day. Most of the vendors were adolescent or young men, but the youngest vendor was aged 8 years and the oldest was aged 50 years. Their clothes were generally unwashed and smelled of gasoline; many of these vendors slept in these clothes. The third group (n = 20) sold heavy oil for motorcycles; using a rubber hose, they sucked about half a liter of gasoline out of motorcycle tanks, mixed it with a similar volume of heavy oil in a tin, and transferred the mixture back to the motorcycle tank. These individuals have been doing this business for prolonged periods and were extremely poorly dressed and smelled of oil and gasoline.

Significant degrees of anemia, neutropenia, and thrombocytopenia were observed in these roadside vendors compared with adolescent (n = 49) and adult (n = 80) control subjects. Motor mechanics (n = 57) working at small repair shops were also at risk of anemia through exposure to gasoline products, which they used freely as solvents and skin cleansers. The attendants at the modern filling stations showed no significant hematologic differences from the control group, confirming that this occupation in Nigeria is probably as safe as has been reported in other countries.

Our observations showed a high prevalence of blood dyscrasias among the roadside vendors and motor mechanics. These dyscrasias were certainly premalignant, so that some of the subjects will eventually develop aplastic anemia, acute myeloid leukemia, or non-Hodgkin's lymphoma.

Globally, the uncontrolled exposure to gasoline probably makes an important contribution to the incidence of hematologic malignancies among the economically deprived. There is an urgent need for legislation, public health control measures, and the greater use of gasoline pumps meeting safety standards to protect these young males.

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